JOC*Article*

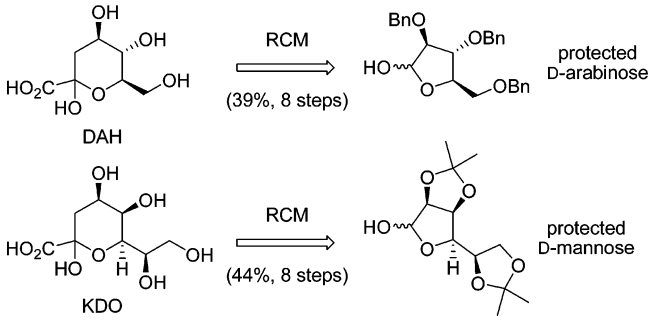
An In-Depth Study on Ring-Closing Metathesis of Carbohydrate-Derived α-Alkoxyacrylates: Efficient Syntheses of DAH, KDO, and 2-Deoxy-β-KDO

Koen F. W. Hekking, Marcel A. H. Moelands, Floris L. van Delft, and Floris P. J. T. Rutjes*

Institute for Molecules and Materials, Radboud University Nijmegen, Toernooiveld 1, NL-6525 ED Nijmegen, The Netherlands

F.Rutjes@science.ru.nl

Received May 3, 2006

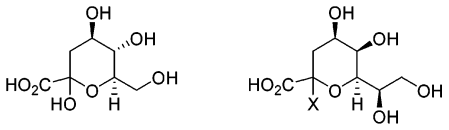


Novel, efficient synthetic pathways to DAH, KDO, and 2-deoxy-β-KDO are described. Ring-closing metathesis (RCM) of highly functionalized α-alkoxyacrylate fragments resulted in a series of synthetically versatile oxygen heterocyclic intermediates. Further functionalization of the resulting enol ether double bond and subsequent deprotection provided the natural products in high overall yields, starting from commercially available protected sugars.

Introduction

The 3-deoxy-2-ulosonic acids constitute a family of carbohydrates that are encountered in a wide variety of biological systems (Chart 1). For instance, 3-deoxy-D-arabino-2-heptulosonic acid (DAH, **1**) is a key intermediate in the biosynthesis of aromatic metabolites in plants and microorganisms (Shikimate pathway). It is formed through stereoselective condensation of phosphoenolpyruvate with D-erythrose by DAHP synthase and transformed in a series of steps to dehydroquinate by the enzyme dehydroquinate synthase.[1] Furthermore, 3-deoxy-D-manno-2-octulosonic acid (KDO, **2**) is an essential component of the cell wall lipopolysaccharides (LPS) of gram-negative bacteria.[2] Activation of KDO by the enzyme CMP−KDO synthase (CKS) is believed to be the rate-determining step in the biosynthesis of LPS,[3] thereby rendering it an interesting target in the development of antibiotics. For example, 2-deoxy-β-KDO (**3**) has been reported as a potent inhibitor of CKS.[4]

CHART 1. Structures of DAH, KDO, and 2-Deoxy-KDO



The rapid increase in drug-resistant bacteria clearly emphasizes the need for development of new classes of antibiotics. Therefore, it is not surprising that the development of efficient synthetic routes to 3-deoxy-2-ulosonic acids and derivatives is of broad interest.[5−8]

(1) (a) Haslam, E. *Shikimic Acid: Metabolism and Metabolites*; Wiley: New York, 1993. (b) Bentley, R. *Crit. Rev. Biochem. Mol. Biol.* **1990**, *25*, 307. (c) Coggins, J. R.; Abell, C.; Evan, L. B.; Frederickson, M.; Robinson, D. A.; Roszak, A. W.; Lapthorn, A. P. *Biochem. Soc. Trans.* **2003**, *31*, 548.

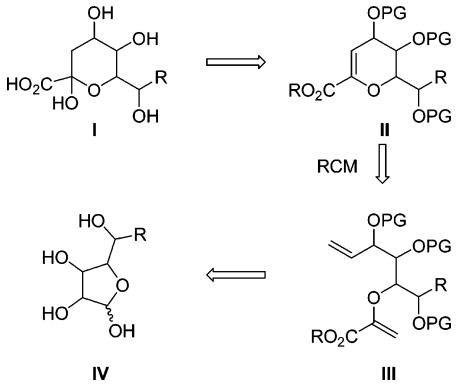
(2) Unger, F. M. *Adv. Carbohydr. Chem. Biochem.* **1981**, *38*, 323 and references therein.

(3) (a) Ray, P. H.; Benedict, C. D.; Grasmuk, H. *J. Bacteriol.* **1981**, *145*, 1283. (b) Goldman, R. C.; Bolling, T. J.; Kohlbrenner, W. E.; Kim, Y.; Fox, J. L. *J. Biol. Chem.* **1986**, *261*, 15831.

(4) (a) Hammond, S. M.; Claesson, A.; Jansson, A. M.; Larsson, L.-G.; Pring, B. G.; Town, C. M.; Ekström, B. *Nature* **1987**, 327, 730. (b) Claesson, A.; Luthman, K.; Gustafsson, K.; Bondesson, G. *Biochem. Biophys. Res. Commun.* **1987**, 143, 1063.

10.1021/jo060913x CCC: $33.50
Published on Web 07/26/2006

SCHEME 1. Retrosynthetic Route to 3-Deoxy-2-ulosonic Acids

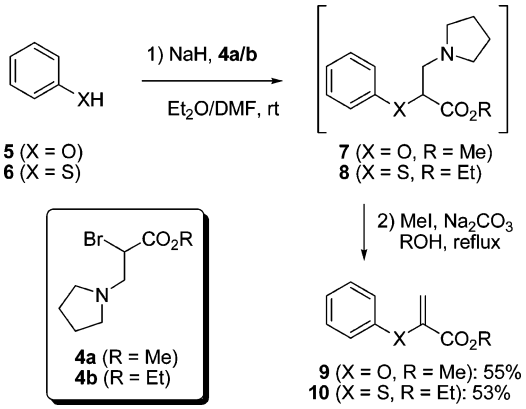


Ring-closing metathesis (RCM) of highly functionalized carbohydrate-derived olefins has received broad attention over the past years, often leading to biologically relevant oxygen heterocycles.[9,10] In this contribution, we report short and efficient total syntheses of KDO and DAH via an RCM-mediated pathway, starting from natural sugars (**IV**, Scheme 1). Key steps in the synthetic route include ring-closing metathesis (RCM) of α-alkoxyacrylates **III**—recently developed in our group[10]—and functionalization of the resulting unsaturated heterocycles **II** via the corresponding iodohydrins.

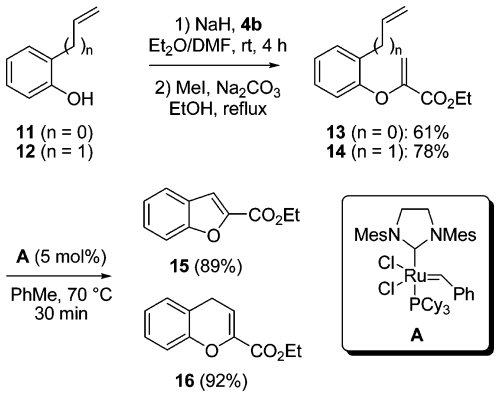
Results and Discussion

Preparation of the metathesis precursors, more specifically the required α-alkoxyacrylate fragments, appeared not to be straightforward. At the time that this research was initiated, only one suitable pathway had been reported. This method involves a laborious three-step procedure, based on a carbene insertion using dimethyl diazomalonate, followed by alkylation with Eschenmoser's salt and subsequent elimination/decarboxylation, with typical overall yields of 25−40%.[11] During our search for shorter and more efficient pathways to these fragments, we developed a synthetic method based on bromides **4a** and **b**, which are readily available from the corresponding 2,3-dibromides. A single preliminary example of this synthetic route was previously described.[10] To optimize the conditions and to investigate the scope of this methodology, we decided to apply this sequence to phenol (**5**) and thiophenol (**6**, Scheme 2). Gratifyingly, the reaction of **5** and **6** with **4a** or **b** followed by *N*-methylation and subsequent base-induced elimination proceeded well, resulting in α-alkoxyacrylate **9** and α-alkylthioacrylate **10** in overall yields of 55% and 53%, respectively. In addition to our earlier findings, we found isolation of intermediates **7** and **8** to be unnecessary. Instead, a single extraction between the substitution and the methylation/elimination steps was sufficient for the overall reaction sequence to proceed efficiently.

SCHEME 2. Formation of Functionalized Acrylates



SCHEME 3. RCM of Alkoxyacrylates



As expected, applying these conditions to ortho-substituted phenols **11** and **12** resulted in the formation of RCM-precursors **13** and **14** in satisfactory yields of 61 and 78%, respectively (Scheme 3). Subsequent ring-closing metathesis proceeded rapidly within 30 min, using the second generation Grubbs catalyst (**A**) in toluene at 70 °C. The resulting benzofuran carboxylate (**15**) and benzopyran carboxylate (**16**) were isolated in excellent yields of 89 and 92%. Interestingly, no olefin isomerization was observed prior to the cyclization of **14**. This is somewhat surprising, since previously reported comparable model systems were found to be prone to isomerization under metathesis conditions.[10,12]

With the availability of a suitable procedure for the synthesis of α-alkoxyacrylate functionalities, the stage was set for

(5) For a recent review on syntheses of 3-deoxy-2-ulosonic acids, see Li, L.-S.; Wu, Y.-L. *Curr. Org. Chem.* **2003**, 7, 447.

(6) For recent syntheses of DAH, see the following: (a) Crestia, D.; Demuynck, C.; Bolte, J. *Tetrahedron* **2004**, *60*, 2417. (b) Liu, K.-G.; Hu, S.-G.; Wu, Y.; Yao, Z.-J.; Wu, Y.-L. *J. Chem. Soc., Perkin Trans. 1* **2002**, 1890. (c) Wardrop, D., J.; Zhang, W. *Tetrahedron Lett.* **2002**, *43*, 5389. (d) Reiner, M.; Stolz, F.; Schmidt, R. R. *Eur. J. Org. Chem.* **2002**, 57. (e) Li, L.-S.; Wu, Y.; Wu, Y.-L. *J. Carbohydr. Chem.* **1999**, *18*, 1067. (f) Dondoni, A.; Marra, A.; Merino, P. *J. Am. Chem. Soc.* **1994**, *116*, 3324.

(7) Recent syntheses of KDO can be found in the following: (a) Kikelj, V.; Plantier-Royon, R.; Portella, C. *Synthesis* **2006**, 1200. (b) Kim, B. G.; Schilde, U.; Linker, T. *Synthesis* **2005**, 1507. (c) Hartmann, K.; Kim, B. G.; Linker, T. *Synlett* **2004**, 2728. (d) Kuboki, A.; Tajimi, T.; Tokuda, Y.; Kato, D.; Sugai, T.; Ohira, S. *Tetrahedron Lett.* **2004**, *45*, 4545. (e) ref 6a. (f) Li, L.-S.; Wu, Y.-L. *Tetrahedron* **2002**, *58*, 9049. (g) ref 6c. (h) Barco, A.; Bassetti, L.; Benetti, S.; Bertolasi, V.; De Risi, C.; Marchetti, P.; Pollini, G. P. *Tetrahedron* **2002**, *58*, 8553.

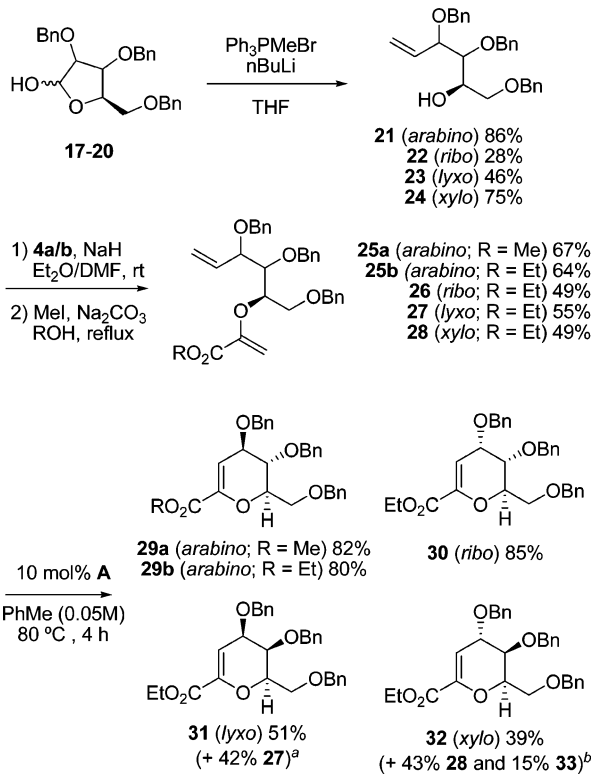
(8) Recent syntheses of 2-deoxy-*β*-KDO can be found in the following: (a) Kumaran, G.; Mootoo, D. R. *Tetrahedron Lett.* **2001**, *42*, 3783. (b) Mlynarski, J.; Banaszek, A. *Org. Lett.* **1999**, *1*, 1709. (c) Burke, S. D.; Sametz, G. M. *Org. Lett.* **1999**, *1*, 71.

(9) (a) Roy, R.; Das, S. K. *Chem. Commun.* **2000**, 519 and references therein (b) Jørgensen, M.; Hadwiger, P.; Madsen, R.; Stütz, A. E.; Wrodnigg, T. M. *Curr. Org. Chem.* **2000**, *4*, 565 and references therein. (c) Postema, M. H. D.; Piper, J. L.; Betts, R. L.; Valeriote, F. A.; Pietraszkewicz, H. *J. Org. Chem.* **2005**, *70*, 829. (d) Postema, M. H. D.; Piper, J. L.; Komanduri, V.; Liu, L. *Angew. Chem., Int. Ed.* **2004**, *43*, 2915. (e) Ovaa, H.; Leeuwenburgh, M. A.; Overkleeft, H. S.; van der Marel, G. A.; van Boom, J. H. *Tetrahedron Lett.* **1998**, *39*, 3025.

(10) Hekking, K. F. W.; van Delft, F. L.; Rutjes, F. P. J. T. *Tetrahedron* **2003**, *59*, 6751.

(11) Gajewski, J. J.; Jurayj, J.; Kimbrough, D. R.; Gande, M. E.; Ganem, B.; Carpenter, B. K. *J. Am. Chem. Soc.* **1987**, *109*, 1170.

SCHEME 4. Preparation of Functionalized Heterocycles via RCM

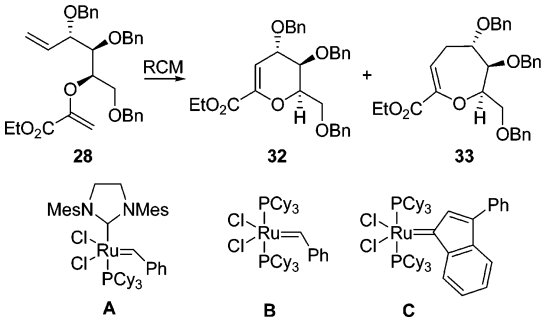


[a] Reaction time was 20 h; the catalyst was added portionwise. [b] 20 mol % of catalyst was used and added portionwise.

application of this methodology in the synthesis of DAH (**1**) and derivatives. Scheme 4 shows the preparation of the functionalized precursors for **1**, as well as analogues with a ribo-, lyxo-, and xylo-configuration. Alcohols **21**−**24** were prepared from the protected sugars **17**−**20**[13] under standard Wittig conditions, following known procedures.[14] Next, the alcohol groups were converted into α-alkoxyacrylate moieties to generate the RCM-precursors **25**−**28** in isolated yields of 49−67%. This transformation was carried out using the two-step procedure described above, involving bromides **4a**,**b**.

Gratifyingly, RCM of **25a**,**b** and **26** proceeded readily using the second generation Grubbs catalyst (**A**) in toluene at 80 °C. Considering the highly functionalized nature of the olefins, the heterocycles **29a**,**b** and **30** were isolated in remarkably good yields of 82%, 80%, and 85%, respectively. On the other hand, olefin **27** reacted significantly slower under these conditions. After portionwise addition of the catalyst and a prolonged reaction time, **31** could be isolated in a yield of 51%. Interestingly, an unexpected side reaction was observed in the cyclization of xylo-derivative **28**. Moreover, the reaction appeared to come to an end at a certain conversion, leaving a

TABLE 1. Ring-Closing Metathesis and Homologation of 28[a]



entry	catalyst (mol %)	concn (M)	**32** (%)	**33** (%)	**32**/**33**	**28** (%)
1	**A** (20)	0.05	39	15	2.6:1	43
2	**A** (20)	0.02	52	19	2.7:1	25
3	**A** (100)	0.05	31	24	1.3:1	n.d.[d]
4	**A** (100)	0.02	47	40	1.2:1	n.d.
5[b]	**A** (100)	0.02	56	36	1.5:1	n.d.
6	**B** (20)	0.02	15[c]	11[c]	1.4:1	74[c]
7	**C** (20)	0.02	18[c]	13[c]	1.4:1	69[c]

[a] Conditions: solution in toluene, inert atmosphere, 80 °C, 18 h. [b] At 60 °C. [c] Based on ^{1}H NMR. [d] n.d. = not determined.

significant amount (43%) of unreacted starting material behind. Although the side product could not be separated from the major product **32** by silica gel chromatography, both compounds were eventually obtained in analytically pure form through preparative HPLC. After extensive investigation of the analytical data, the side-product was identified as the seven-membered ring **33** (Table 1).

This observation implies that a methylene group is introduced during the RCM process, which to the best of our knowledge, is unprecedented in ring-closing olefin metathesis. The observation of such an "insertion mechanism" sharply contrasts with the frequently observed "deletion mechanism" where ethylene is lost, caused by olefin isomerization prior to cyclization.[15] Interestingly, when a mixture of the two products was resubjected to the metathesis conditions, the ratio did not change. This suggests that the one-carbon homologation takes place in the starting compound **28** prior to cyclization. Carrying out the reaction at different temperatures and/or concentrations did not significantly influence the ratio between **32** and **33**, although lower concentrations clearly resulted in higher conversion of the starting material (Table 1, entries 1 and 2). On the other hand, in case 1 equiv of **A** was used, the ratio **32**/**33** changed from 2.6:1 to 1.2−1.5:1 (entries 3 to 5). Finally, the first generation catalysts **B** and **C** also produced **33** as a side product, albeit with low conversions (entries 6 and 7).

A tentative mechanism for this transformation has recently been foreseen by others on the basis of DFT calculations on ruthenacyclobutane intermediates.[16] This mechanistic pathway involves β-hydrogen elimination from the known metathesis

(12) Recently, Grubbs and co-workers reported that the addition of metal hydride scavengers can prevent isomerization during olefin metathesis: Hong, S. H.; Sanders, D. P.; Lee C. W.; Grubbs, R. H. *J. Am. Chem. Soc.* **2005**, *127*, 17160.

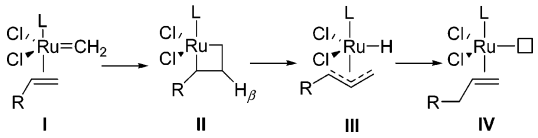
(13) Protected sugar **17** was commericially available; **18**−**20** were prepared using known protection procedures: Barker, R.; Fletcher, H. G. *J. Org. Chem.* **1961**, *26*, 4605.

(14) (a) Postema, M. H. D.; Calimente, D.; Liu, L.; Behrmann, T. L. *J. Org. Chem.* **2000**, *65*, 6061. (b) Pearson, W. H.; Hines, J. V. *J. Org. Chem.* **2000**, *65*, 5785. (c) Freeman, F.; Robarge, K. D. *Carbohydr. Res.* **1986**, *154*, 270.

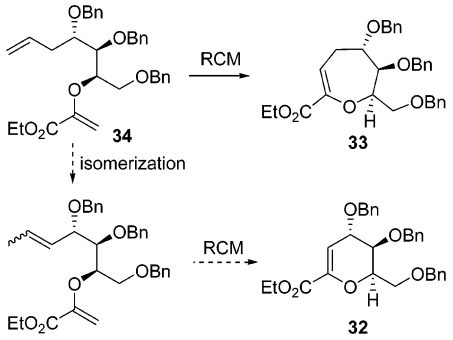
(15) (a) Schmidt, B. *Eur. J. Org. Chem.* **2004**, 1865. (b) Bourgeois, D.; Pancrazi, A.; Nolan, S. P.; Prunet, J. *J. Organomet. Chem.* **2002**, *643*−*644*, 247. (c) Kinderman, S. S.; van Maarseveen, J. H.; Schoemaker, H. E.; Hiemstra, H.; Rutjes, F. P. J. T. *Org. Lett.* **2001** *3*, 2045. (d) Fürstner, A.; Thiel, O. R.; Ackermann, L.; Schanz, H.-J.; Nolan, S. P. *J. Org. Chem.* **2000**, *65*, 2204.

(16) DFT calculations suggested the feasability of this pathway, which was supported experimentally by the generation of propene from ethene: Janse van Rensburg, W.; Steynberg, P. J.; Meyer, W. H.; Kirk, M. M.; Forman, G. S. *J. Am. Chem. Soc.* **2004**, *126*, 14332.

SCHEME 5. Tentative Homologation Mechanism



SCHEME 6. Possible Formation of 32 and 33 from 34



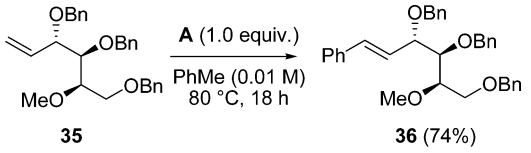
intermediate **II**, resulting in π-allylruthenium(IV) complex **III** (Scheme 5). Reductive elimination to complex **IV** and subsequent dissociation of the olefin from the metal center would then generate the homologated product.

In our case, this would imply that subjection of **28** to this pathway would lead to the homologated RCM-precursor **34**, which gives **33** upon cyclization (Scheme 6). Since a ruthenium carbene species is not regenerated through this sequence, it also represents a decomposition pathway for olefin metathesis catalysts. This is in agreement with (a) the observation of lower total conversions in cases of catalytic amounts of **A** and (b) the fact that the yield of homologated product never exceeds the amount of catalyst used (Table 1).

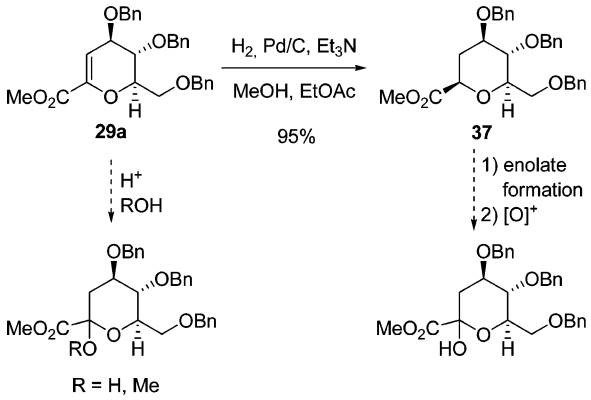
Unfortunately, we have not been able to observe compound **34** by NMR, presumably because of the high reactivity of the relatively unhindered monosubstituted double bond. In addition, we cannot exclude the occurrence of olefin isomerization in **34** under metathesis conditions, eventually resulting in formation of **32** (Scheme 6). Thus, the homologation might in fact be more efficient than the ratio between **32** and **33** initially suggests. To further investigate this assumption, we decided to synthesize compound **35**[17] and subject it to the previously discussed conditions to see whether it would be possible to isolate the homologated product. The lack of a second double bond in **35** eliminates the possibility of cyclization, and we anticipated that the presence of an allylic benzyloxy substituent would inhibit formation of a homodimeric cross-metathesis product,[18] thereby preventing these two reactions to compete with the homologation.

Indeed, no homodimerization took place, but instead, cross-metathesis (CM) of **35** was observed with styrene that presumably originates from catalyst **A** (Scheme 7). The efficient nature of this reaction prevented us from detecting any homologated products. Nevertheless, this outcome is somewhat surprising, especially since this side-reaction is generally not observed in olefin metathesis. Further aspects of the homologation reaction,

SCHEME 7. Cross-Metathesis Instead of Homologation



SCHEME 8. Potential Approaches from 29a to DAH (1)



such as its substrate-dependent behavior, are currently under investigation.[19]

Initial attempts to complete the synthesis of DAH were based on modification of a glycal intermediate in earlier reported syntheses of KDO (Scheme 8).[8c] This involved hydrogenation of **29a** to the saturated counterpart **37**. Next, the lithium enolate could be formed (LDA, THF, −78 °C), but did not exhibit any reactivity toward several electrophilic reagents including MoO_5·Py·HMPA (MoOOPH)[8c,20] and PhSSPh.[21] The lack of further literature precedent inspired us to actually take advantage of the reactivity of the double bond in **29a**. Initially however, attempts to hydrate **29a** under acidic conditions in water led to decomposition. When carried out in methanol, the reaction proceeded extremely slowly and produced only moderate yields of the desired acetal. In addition, hydrolysis of the resulting acetal was found to be problematic, forcing us to abandon this route.

Finally, we were pleased to find that by applying the electrophilic reagent *N*-iodosuccinimide (NIS) in acetonitrile/water,[22] enol ether **29a** was efficiently converted into iodohydrin **38**, which was isolated as a 1:1 mixture of diastereoisomers (Scheme 9). Subsequent removal of the iodide under hydrogenation conditions in the presence of triethylamine gave protected DAH (**39**) in a yield of 83% from **29a**.

Deprotection of **39** proved to be somewhat less trivial than expected. Despite literature precedent,[6c] in our hands removal of the benzyl protective groups did not occur under regular hydrogenation conditions using Pd/C or $Pd(OH)_2$/C, in combination with different solvents and pressures up to 40 bar. Reaction of **39** with BCl_3 did result in debenzylation, but the isolated yields never exceeded 60%. However, when carrying out the hydrogenation procedure with Degussa type Pd/C (H_2O

(17) Compound **35** was synthesized by reacting **28** with NaH and MeI in DMF.

(18) The inhibition of cross-metathesis by allylic ether substituents has been previously reported: (a) Nolen, E. G.; Kurish, A. J.; Potter, J. M.; Donahue, L. A.; Orlando, M. D. *Org. Lett.* **2005**, *7*, 3383. (b) Maishal, T. K.; Sinha-Mahapatra, D. K.; Paranjape, K.; Sarkar, A. *Tetrahedron Lett.* **2002**, *43*, 2263 and references therein.

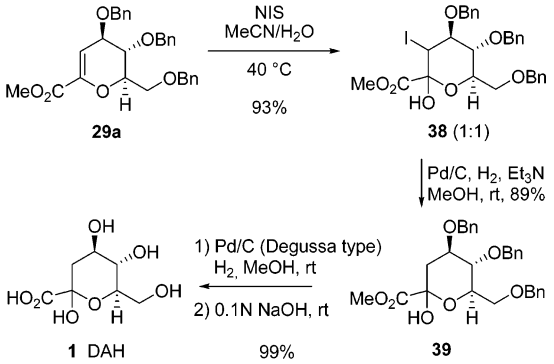
(19) For other nonmetathetic behavior of Grubbs catalyst, see the following: (a) Alcaide, B.; Almendros, P. *Chem. Eur. J.* **2003**, *9*, 1259. (b) Trost, B. M.; Toste, F. D.; Pinkerton, A. B. *Chem. Rev.* **2001**, *101*, 2067.

(20) (a) Vedejs, E.; Engler, D. A.; Telschow, J. E. *J. Org. Chem.* **1978**, *43*, 3, 188. (b) Vedejs, E.; Larsen, S. *Org. Synth.* **1986**, *64*, 127.

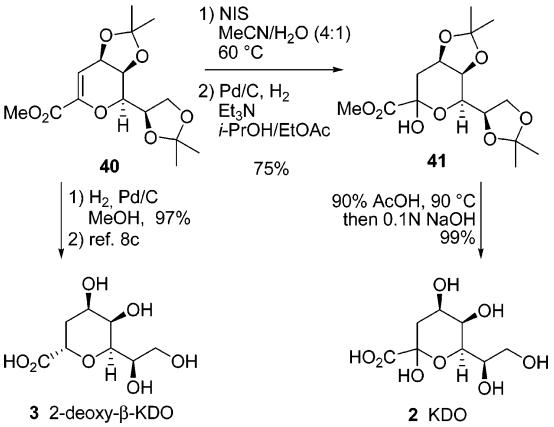
(21) Lubineau, A.; Auge, J.; Lubin, N. *Tetrahedron* **1993**, *49*, 4639.

(22) Kok, G. B.; van Phan, T.; von Itzstein, M. *J. Carbohydr. Chem.* **2001**, *20*, 359.

SCHEME 9. Completion of the Synthesis of DAH (1)



SCHEME 10. Synthesis of KDO (2) and 2-Deoxy-β-KDO (3)



content 50%), complete deprotection took place within 1 h at room temperature and under atmospheric pressure. Saponification of the ester then gave DAH (**1**)[23] in an overall yield of 39% over eight steps, starting from commercially available **17**.

Encouraged by these results, more specifically the straightforward preparation of the glycals and their efficient functionalization, we decided to apply this approach in a total synthesis of KDO (**2**, Scheme 10). The heterocyclic intermediate **40** was prepared in 64% over four steps from protected D-mannose, under similar conditions as **29**−**32**, following our previous report.[10,24]

The potential of these types of glycal intermediates was further demonstrated by quantitative hydrogenation of the double bond in **40**, selectively yielding protected 2-deoxy-α-KDO. This can then be epimerized and deprotected via a reported procedure[8c] to give 2-deoxy-β-KDO (**3**).

Moreover, reaction of glycal **40** with NIS appeared to proceed as anticipated at 60 °C giving rise to the corresponding iodohydrin, although substantial product decomposition was observed when the reaction was left stirring for longer than 4 h. Removal of the iodide demanded certain optimization as well. Triethylamine was required in the hydrogenation to scavenge the liberated HI, but these mildly basic conditions led to partial substitution of the iodide by methanol as well. Switching to a mixture of isopropyl alcohol and ethyl acetate solved this problem so that protected KDO (**41**) could be isolated in a yield of 75% from **40**. This NIS-based conversion now represents a significantly more efficient alternative to the known methods, which rely on enolate formation of the hydrogenated form of **40**, followed by introduction of an oxygen or sulfur electrophile.[8c,21] Perhaps more importantly, this mild method might even be applicable to complex oligosaccharides, in which such a glycal unit is incorporated. Finally, general deprotection conditions converted **41** into KDO (**2**), which was isolated and analyzed as its ammonium salt.[25] The overall yield of KDO (**2**) was 44% over eight steps, starting from commercially available protected D-mannose.

Conclusions

In conclusion, we have shown that ring-closing metathesis of highly substituted α-alkoxyacrylates and subsequent novel functionalization via the iodohydrin represent a short and efficient synthetic pathway to 3-deoxy-2-ulosonic acids. Furthermore, this route includes a high-yielding four-step procedure from protected natural sugars to substituted glycals, which can serve as versatile building blocks for biologically relevant derivatives. The viability of the route was proven by syntheses of the natural products DAH and KDO, as well as that of 2-deoxy-β-KDO, a potent inhibitor of CMP−KDO synthase.

In addition, we have reported the first example of one-carbon homologation in a ring-closing metathesis reaction. This observation provides important new insight into catalyst decomposition during ruthenium-based olefin metathesis. Furthermore, it might open up new possibilities for versatile tandem reaction sequences. Additional aspects of this novel Ru-mediated reaction are currently under investigation.

Experimental Section

General. General experimental details are described in the Supporting Information.

General Procedure A for the Preparation of α-Alkoxyacrylates. To a cooled (0 °C) solution of the alcohol (1 equiv) in diethyl ether/DMF (1:1, 0.05 M) was added NaH (60% in mineral oil; 2.5 equiv), and the mixture was stirred at 40 °C for 1 h. After cooling to room temperature, freshly prepared **4a** or **b** (3.5 equiv) was added, and the reaction was stirred for 18 h. Next, H_2O was added, the mixture was extracted with diethyl ether (3×), and the combined organic layers were concentrated in vacuo. The residue was dissolved in (m)ethanol (0.1 M). MeI (10 equiv) and Na_2CO_3 (5 equiv) were added, and the reaction mixture was allowed to stir at reflux temperature for 48 h. Next, H_2O was added, and the mixture was extracted with CH_2Cl_2 (3×). The combined organic layers were dried with $MgSO_4$ and concentrated, and the product was isolated by column chromatography (EtOAc/heptane, 1:6).

Methyl 2-((2*R*,3*S*,4*R*)-1,3,4-Tris(benzyloxy)hex-5-en-2-yloxy)-acrylate (25a). This compound was synthesized from **21**, following general procedure A. The yield was 708 mg (69%). ^{1}H NMR ($CDCl_3$, 300 MHz): δ 7.32−7.24 (m, 15H), 5.89 (m, 1H), 5.38 (d, J = 2.5 Hz, 1H), 5.32 (m, 2H), 4.72 (d, J = 2.5 Hz, 1H), 4.67 (s, 2H), 4.50 (s, 2H), 4.46 (m, 1H), 4.43 (d_{AB}, J = 11.7 Hz, 2H), 4.04 (m, 1H), 3.91−3.72 (m, 3H), 3.77 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 163.7, 149.8, 138.3, 138.2, 138.1, 135.4, 128.3, 128.2,

(23) Spectroscopic data agreed with those previously reported: (a) ref 6d. (b) Barton, D. H. R.; Liu, W. S. *Tetrahedron* **1997**, *53*, 12067.

(24) Using the optimized procedures described here, we are now able to prepare **40** from protected D-mannose more efficiently (64% compared to 45%), than we initially reported (ref 10). In addition, we found that the use of first-generation catalysts **B** and **C** for the ring-closing metathesis also resulted in cyclization, albeit under more harsh conditions (100 °C) and with lower yields (50−62%).

(25) Spectroscopic data agreed with those of an authentic commercial sample and with those previously reported: (a) Schlessinger, R. H.; Pettus, L. H. *J. Org. Chem.* **1998**, *63*, 9089. (b) Sugai, T.; Shen, G.-J.; Ichikawa, Y.; Wong, C.-H. *J. Am. Chem. Soc.* **1993**, *115*, 413.

128.1 (2), 127.7, 127.6, 127.5 (2), 127.4, 119.0, 96.3, 80.1, 80.0, 77.3, 74.9, 73.3, 70.6, 67.9, 52.2. IR (CH_2Cl_2): ν 3029, 2948, 2865, 1734, 1621 cm^{-1}. $[\alpha]^{22}_D$ −8.6 (*c* 1.3, CH_2Cl_2). HRMS (CI^+): calcd for $C_{31}H_{35}O_6$ $[M + H]^+$, 503.2434; found, 503.2434.

Ethyl 2-((2*R*,3*S*,4*R*)-1,3,4-Tris(benzyloxy)hex-5-en-2-yloxy)-acrylate (25b). This compound was synthesized from **21**, following general procedure A. The yield was 380 mg (68%). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.31−7.24 (m, 15H), 5.89 (m, 1H), 5.38 (d, J = 2.6 Hz, 1H), 5.31 (m, 2H), 4.72 (d, J = 2.6 Hz, 1H), 4.69 (s, 2H), 4.51 (s, 2H), 4.45 (m, 1H), 4.44 (d_{AB}, J = 11.8 Hz, 2H), 4.22 (q, J = 7.2 Hz, 2H), 4.04 (m, 1H), 3.88 (m, 2H), 3.75 (dd, J = 5.1, 10.9 Hz), 1.29 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.9, 149.9, 138.1 (2), 138.0, 135.2, 128.1, 128.0, 127.9, 127.8, 127.4, 127.3, 127.2, 118.8, 96.0, 80.3, 80.2, 77.4, 75.0, 73.3, 70.7, 68.1, 61.3, 14.4. IR (CH_2Cl_2): ν 3030, 2927, 2869, 1727, 1620 cm^{-1}. $[\alpha]^{22}_D$ −6.2 (*c* 0.5, CH_2Cl_2). HRMS (CI^+): calcd for $C_{32}H_{37}O_6$ $[M + H]^+$, 517.2590; found, 517.2597.

Ethyl 2-((2*R*,3*S*,4*S*)-1,3,4-Tris(benzyloxy)hex-5-en-2-yloxy)-acrylate (26). This compound was synthesized from **22**, following general procedure A. The yield was 27 mg (49%). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.30−7.15 (m, 15H), 5.89−5.75 (m, 1H), 5.40 (d, J = 2.7 Hz, 1H), 5.37−5.21 (m, 2H), 4.80 (d, J = 2.1 Hz, 1H), 4.69 (s, 2H), 4.49 (s, 2H), 4.47−4.45 (m, 1H), 4.48 (d_{AB}, J = 11.6 Hz, 2H), 4.24 (q, J = 6.9 Hz, 2H), 4.00 (dd, J = 6.0, 7.5 Hz, 1H), 3.93 (dd, J = 4.5, 6.0 Hz, 1H), 3.83−3.70 (m, 2H), 1.29 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 163.0, 150.0, 138.2, 138.1, 135.3, 128.1 (2), 128.0, 127.4 (3), 127.3 (2), 119.5, 96.3, 80.7, 79.6, 78.1, 74.4, 73.3, 70.5, 68.5, 61.3, 14.4. IR (CH_2Cl_2): ν 3023, 2920, 1722, 1623 cm^{-1}. $[\alpha]^{25}_D$ +20.3 (*c* 0.2, CH_2Cl_2). HRMS (CI^+): calcd for $C_{32}H_{37}O_6$ $[M + H]^+$, 517.2590; found, 517.2593.

Ethyl 2-((2*R*,3*R*,4*R*)-1,3,4-Tris(benzyloxy)hex-5-en-2-yloxy)-acrylate (27). This compound was synthesized from **23**, following the general procedure. The yield was 272 mg (55%). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.32−7.17 (m, 15H), 6.01−5.90 (m, 1H), 5.45−5.37 (m, 2H), 5.24 (d, J = 2.4 Hz, 1H), 4.71−4.44 (m, 6H), 4.38 (d, J = 2.7 Hz, 1H), 4.26−4.11 (m, 4H), 3.76−3.68 (m, 3H), 1.30 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.6, 150.9, 138.3, 138.1, 137.9, 136.0, 128.3, 128.1 (2), 128.0 (2), 127.5 (2), 127.4, 127.3, 127.0, 119.4, 94.0, 80.7, 80.0, 76.4, 74.3, 73.6, 70.2, 69.2, 61.3, 14.4. IR (CH_2Cl_2): ν 3022, 2868, 1723, 1619 cm^{-1}. $[\alpha]^{25}_D$ −17.7 (*c* 1.5, CH_2Cl_2). HRMS (CI^+): calcd for $C_{32}H_{37}O_6$ $[M + H]^+$, 517.2590; found, 517.2607.

Ethyl 2-((2*R*,3*R*,4*S*)-1,3,4-Tris(benzyloxy)hex-5-en-2-yloxy)-acrylate (28). This compound was synthesized from **24**, following general procedure A. The yield was 33 mg (49%). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.35−7.19 (m, 15H), 5.92−5.77 (m, 1H), 5.33 (d, J = 2.5 Hz, 1H), 5.24 (m, 2H), 4.73 (m, 2H), 4.71 (d, J = 2.7 Hz, 1H), 4.40 (d_{ab}, J = 11.7 Hz, 2H), 4.41−4.13 (m, 5H), 4.08 (dd, J = 5.3, 7.7 Hz, 1H), 3.78 (t, J = 5.1 Hz, 1H), 3.69−3.43 (m, 2H), 1.28 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 163.0, 150.6, 138.4, 138.0, 137.8, 135.1, 128.1(2), 128.0, 127.9, 127.5-(2), 127.3(2), 118.9, 96.1, 80.9, 80.4, 78.7, 75.0, 73.3, 70.6, 67.7, 61.3, 14.4. IR (CH_2Cl_2): ν 3023, 2863, 1722, 1619 cm^{-1}. $[\alpha]^{25}_D$ +1.3 (*c* 0.8, CH_2Cl_2). HRMS (CI^+): calcd for $C_{32}H_{37}O_6$ $[M + H]^+$, 517.2590; found, 517.2588.

General Procedure B for Ring-Closing Metathesis. To a solution of the α-alkoxy acrylate in toluene (0.05 M) was added 10 mol % of $(IMes)(PCy_3)Cl_2Ru{=}CHPh$ (**A**), and the mixture was stirred under an inert atmosphere at 80 °C for 4 h. The reaction was ended by exposure to air and removal of the solvent in vacuo. The product was purified by column chromatography (EtOAc/heptane, 1:6).

(4*R*,5*S*,6*R*)-Methyl 4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-5,6-dihydro-4*H*-pyran-2-carboxylate (29a). This compound was synthesized from **25a**, following general procedure B. The yield was 529 mg (82%). The analytical data agreed with literature data.[26] ^1H NMR ($CDCl_3$, 300 MHz): δ 7.34−7.25 (m, 15H), 6.11 (d, J = 3.1 Hz, 1H), 4.82−4.53 (m, 6H), 4.28 (dd, J = 3.1, 6.2 Hz, 1H), 4.19 (m, 1H), 3.95 (dd, J = 6.2, 8.6 Hz, 1H), 3.84 (d, J = 3.8 Hz, 2H), 3.81 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.6, 144.3, 138.0, 137.9, 137.8, 128.5, 128.4, 128.3, 127.9, 127.8 (3), 127.6, 108.3, 77.8, 75.4, 73.8, 73.5 (2), 70.9, 67.7, 52.4. $[\alpha]^{22}_D$ −9.6 (*c* 0.5, CH_2Cl_2).

(4*R*,5*S*,6*R*)-Ethyl 4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-5,6-dihydro-4*H*-pyran-2-carboxylate (29b). This compound was synthesized from **25b**, following general procedure B. The yield was 77 mg (80%). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.34−7.24 (m, 15H), 6.08 (d, J = 3.1 Hz, 1H), 4.82−4.55 (m, 6H), 4.30−4.16 (m, 2H), 4.26 (q, J = 7.2 Hz, 2H), 3.94 (dd, J = 6.1, 8.4 Hz, 1H), 3.84 (d, J = 3.8 Hz, 2H), 1.32 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 161.8, 144.2, 137.8, 137.7, 137.6, 128.2 (2), 128.1, 127.7, 127.6 (2), 127.5, 127.4, 107.8, 77.7, 75.5, 73.8, 73.5, 73.4, 71.0, 67.7, 61.5, 14.4. IR (CH_2Cl_2): ν 3029, 2866, 1733, 1652 cm^{-1}. $[\alpha]^{22}_D$ −5.9 (*c* 0.5, CH_2Cl_2). HRMS (CI^+): calcd for $C_{30}H_{33}O_6$ $[M + H]^+$, 489.2277; found, 489.2277.

(4*S*,5*S*,6*R*)-Ethyl 4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-5,6-dihydro-4*H*-pyran-2-carboxylate (30). This compound was synthesized from **26**, following the general procedure. The yield was 17 mg (85%). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.34−7.24(m, 15H), 6.05 (d, J = 5.5 Hz, 1H), 4.72−4.50 (m, 6H), 4.35 (dt, J = 2.9, 10.0 Hz, 1H), 4.24 (q, J = 7.1 Hz, 2H), 4.03 (dd, J = 3.8, 5.7 Hz, 1H), 3.88 (d, J = 3.1 Hz, 2H), 3.83 (dd, J = 3.8, 10.0 Hz, 1H), 1.31 (t, J = 7.1 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 161.9, 145.5, 138.0, 137.9, 137.5, 128.2, 127.8 (2), 127.5, 106.0, 74.4, 73.5, 72.9, 71.8, 71.2, 68.2, 65.9, 61.5, 14.4. IR (CH_2Cl_2): ν 3020, 2872, 1732, 1645 cm^{-1}. $[\alpha]^{25}_D$ +200.5 (*c* 0.2, CH_2Cl_2). HRMS (CI^+): calcd for $C_{30}H_{32}O_6$ $[M]^+$, 488.2199; found, 488.2198.

(4*R*,5*R*,6*R*)-Ethyl 4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-5,6-dihydro-4*H*-pyran-2-carboxylate (31) This compound was synthesized from **27**, following general procedure B. The catalyst was added portionwise over 4 h, and the total reaction time was 20 h. The yield was 48 mg (51%), and 37 mg (42%) of starting material was recovered. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.30−7.18 (m, 15H), 6.25 (d, J = Hz, 1H), 4.59−4.43 (m, 6H), 4.24 (q, J = 7.1 Hz, 2H),4.42 (m, 2H), 4.15 (m, 1H), 3.85 (m, 2H), 1.30 (t, J = 7.1 Hz, 3H). $[\alpha]^{25}_D$ −58.9 (*c* 0.1, CH_2Cl_2). HRMS (CI^+): calcd for $C_{30}H_{33}O_6$ $[M + H]^+$, 489.2277; found, 489.2275.[27]

(4*S*,5*R*,6*R*)-Ethyl 4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-5,6-dihydro-4*H*-pyran-2-carboxylate (32) and (5*S*,6*R*,7*R*)-Ethyl 5,6-Bis(benzyloxy)-7-(benzyloxymethyl)-4,5,6,7-tetrahydrooxepine-2-carboxylate (33). The reaction was carried out according to general procedure B, using **28** and 20 mol % of catalyst, which was added portionwise. ^1H NMR showed a mixture of two products in a ratio of 1:0.45, which could not be separated by column chromatography. After separation by preparative HPLC, the isolated products were identified as **32** (major) and **33** (minor). The combined yield was 54%.

Compound 32. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.36−7.21 (m, 15H), 6.12 (dd, J = 1.5, 5.1 Hz, 1H), 4.59−4.43 (m, 6H), 4.23 (q, J = 7.2 Hz, 2H), 4.17 (m, 1H), 3.84 (m, 2H), 3.75 (m, 2H), 1.30 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 162.3, 145.8, 138.0, 137.9, 137.6, 128.5, 128.4 (2), 128.2, 128.0, 127.9, 127.7 (2), 106.5, 73.9, 73.4, 72.5, 71.8, 70.5, 67.8, 67.7, 61.4, 14.1. IR (CH_2Cl_2): ν 3022, 2930, 1726, 1637 cm^{-1}. $[\alpha]^{22}_D$ +61.2 (*c* 0.24, CH_2Cl_2). HRMS (EI^+): calcd for $C_{30}H_{32}O_6$ $[M]^+$, 488.2199; found, 488.2190.

Compound 33. ^1H NMR ($CDCl_3$, 400 MHz): δ 7.32−7.25 (m, 15H), 6.17 (dd, J = 5.0, 7.0 Hz, 1H), 4.75−4.47 (m, 6H), 4.30 (dt, J = 1.9, 6.6 Hz, 1H), 4.18 (q, J = 7.2 Hz, 2H), 3.89 (m, 2H), 3.79 (dd, J = 5.5, 10.0 Hz, 1H), 3.71 (dd, J = 6.6, 10.0 Hz, 1H), 2.60 (ddd, J = 2.3, 7.0, 17.1 Hz, 1H), 2.48 (ddd, J = 5.0, 8.9, 17.1 Hz), 1.25 (t, J = 7.2 Hz, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 163.4, 149.3, 138.3, 138.2, 138.0, 128.4, 128.3 (2), 128.0, 127.8, 127.7

(26) Crich, D.; Ritchie, T. J. *J. Chem. Soc., Perking Trans. 1* **1990**, 945.

(27) Rapid deterioration of the product during or immediately after column chromatography prevented further characterization.

(2), 127.6 (2), 115.8, 81.1, 80.1, 78.4, 73.9, 73.5, 71.6, 69.1, 61.1, 27.0, 14.2. IR (CH_2Cl_2): ν 3052, 2985, 1717, 1649 cm^{-1}. $[\alpha]^{22}_D$ +4.5 (*c* 0.11, CH_2Cl_2). HRMS (EI^+): calcd for $C_{31}H_{35}O_6$ $[M+H]^+$, 503.2434; found, 503.2427.

(4*S*,5*S*,6*R*)-Methyl 4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-2-hydroxy-3-iodo-tetrahydro-2*H*-pyran-2-carboxylate (38). A solution of **29a** (425 mg, 0.896 mmol) and *N*-iodosuccinimide (301 mg, 1.34 mmol) in MeCN (25 mL) and H_2O (10 mL) was stirred for 4 h at 40 °C. Next, the solvent was removed in vacuo, and the products were purified by column chromatography (EtOAc/heptane, 1:6). The product was isolated as a mixture (~1:1) of two diastereoisomers. A small portion of the mixture was separated for analytical purposes. The combined yield of both isomers was 514 mg (93%).

First Diastereoisomer. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.43−7.15 (m, 15H), 4.99−4.79 (m, 3H), 4.59−4.35 (m, 4H), 4.12 (m, 1H), 4.02 (dd, J = 9.0, 11.5 Hz, 1H), 3.89 (s, 3H), 3.73 (m, 2H), 3.62 (dd, J = 2.0, 11.3 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.9, 138.0, 137.8 (2), 128.4 (2), 128.3, 128.0, 127.9, 127.8, 127.7 (2), 127.6, 96.1, 82.2, 79.3, 75.5, 75.0, 74.2, 73.4, 68.2, 54.0, 30.8. $[\alpha]^{22}_D$ +3.9 (*c* 0.9, CH_2Cl_2).

Second diastereoisomer. ^1H NMR ($CDCl_3$, 300 MHz): δ 7.41−7.14 (m, 15H), 4.88−4.48 (m, 7H), 4.09 (m, 2H), 3.88−3.72 (m, 3H), 3.84 (s, 3H), 3.46 (dd, J = 4.1, 8.7 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 168.9, 138.2, 138.0, 137.5, 128.4, 128.3 (2), 128.1, 128.0, 127.9 (2), 127.7, 127.5, 96.9, 76.7, 75.7, 75.2, 74.0, 73.4, 70.8, 68.7, 53.1, 35.0. $[\alpha]^{22}_D$ −10.1 (*c* 0.9, CH_2Cl_2).

Mixture. IR (CH_2Cl_2): ν 3030, 2981, 2870, 1725, 1264, 1186 cm^{-1}. HRMS (ESI^+): calcd for $C_{29}H_{31}O_7INa$ $[M+Na]^+$, 641.1012; found, 641.1000.

(4*R*,5*S*,6*R*)-Methyl 4,5-Bis(benzyloxy)-6-(benzyloxymethyl)-2-hydroxy-tetrahydro-2*H*-pyran-2-carboxylate (39). A solution of **38** (49.5 mg, 80.0 μmol) and Et_3N (35 μL, 0.25 mmol) in MeOH (8 mL) was treated with 10% Pd/C (9 mg) and H_2 (1 atm) for 18 h. After the reaction, the mixture was filtered over Celite and concentrated, and the product was purified by column chromatography (EtOAc/heptane, 1:4). The yield was 35 mg (89%). ^1H NMR ($CDCl_3$, 300 MHz): δ 7.33−7.17 (m, 15H), 4.92−4.48 (m, 6H), 4.03 (m, 2H), 3.83 (s, 3H), 3.78−3.64 (m, 3H), 3.60 (dd, J = 9.0, 9.8 Hz, 1H), 2.28 (dd, J = 5.0, 12.6 Hz, 1H), 2.09 (t, J = 12.2 Hz, 1H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 170.0, 138.2 (2), 138.0, 128.2, 128.1, 127.7, 127.6, 127.5, 127.4 (2), 94.9, 78.0, 77.6, 75.0, 73.4, 73.1, 71.9, 69.0, 53.4, 36.3. IR (CH_2Cl_2): ν 3052, 2987, 1754 cm^{-1}. $[\alpha]^{22}_D$ +46.0 (*c* 0.2, CH_2Cl_2). HRMS (CI^+): calcd for $C_{29}H_{32}O_7$ $[M + H]^+$, 493.2226; found, 493.2228.

3-Deoxy-D-arabino-2-heptulopyranosonic Acid (DAH, 1). A solution of **39** (6.2 mg, 12.6 μmol) in MeOH (1.5 mL) was treated with 10% Pd/C (Degussa type E101 NE/W, H_2O content 50%; 3 mg) and H_2 (1 atm) for 1 h. ^1H NMR of the reaction mixture showed a quantitative conversion, and the mixture was filtered over Celite and concentrated. The resulting DAH methyl ester was dissolved in 1 N NaOH (4 mL) and stirred at room temperature for 1 h. The mixture was neutralized with Amberlyte IR-120$^+$, filtered, and concentrated. The resulting solid was washed with EtOAc and dried, giving **1** in a yield of 2.6 mg (99%). The analytical data were in agreement with reported data.[23] ^1H NMR (D_2O, 400 MHz): δ 3.92−3.98 (m, 1H), 3.84−3.74 (m, 3H), 3.45 (t, J = 9.3 Hz, 1H, 5-H), 2.20 (dd, J = 5.1, 13.0 Hz, 1H, 3-H), 1.79 (t, J = 12.5 Hz, 1H, 3-H). $[\alpha]^{22}_D$ +41.5 (*c* 0.25, D_2O).

(3a*R*,4*R*,7a*R*)-Methyl 4-((*R*)-2,2-Dimethyl-1,3-dioxolan-4-yl)-6-hydroxy-2,2-dimethyl-tetrahydro-3a*H*-[1,3]dioxolo[4,5-c]pyran-6-carboxylate (41). A solution of **40** (40 mg, 0.128 mmol) and *N*-iodosuccinimide (63 mg, 0.282 mmol) in MeCN (6 mL) and H_2O (1.5 mL) was stirred for 2 h at 60 °C. Next, the solvent was removed in vacuo, and the product was purified by column chromatography (EtOAc/heptane, 1:6), yielding 53 mg (91%) of the iodohydrin. The product was a single isomer, the absolute configuration of which was not determined. ^1H NMR ($CDCl_3$, 300 MHz): δ 4.56 (dd, J = 5.0, 9.5 Hz, 1H), 4.35 (m, 2H), 4.26−4.15 (m, 3H), 4.04−3.88 (m, 2H), 3.88 (s, 3H), 1.55 (s, 3H), 1.20 (s, 3H), 1.39 (s, 3H), 1.34 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 163.1, 109.4 (2), 95.9, 78.2, 73.8, 73.2, 70.0, 66.8, 54.2, 30.4, 28.6, 27.1, 26.4, 25.6. HRMS (CI^+): calcd for $C_{15}H_{24}O_8I$ $[M + H]^+$, 459.0516; found, 459.0501. A solution of the iodohydrin (53 mg, 0.116 mmol) and Et_3N (18 μL, 0.127 mmol) in EtOAc (5 mL) and *i*-PrOH (5 mL) was treated with 10% Pd/C (7 mg) and H_2 (1 atm) for 18 h. After the reaction, the mixture was filtered over Celite and concentrated, and the product was purified by column chromatography (EtOAc/heptane, 1:4). The yield was 32 mg (75% from **40**). The analytical data agreed with those reported in the literature.[28] ^1H NMR ($CDCl_3$, 300 MHz): δ 4.49 (m, 1H), 4.34 (ddd, J = 4.5, 6.2, 8.3 Hz, 1H), 4.25 (dd, J = 2.4, 6.4 Hz, 1H), 4.07 (dd, J = 6.2, 8.8 Hz, 1H), 3.97 (dd, J = 4.5, 8.8 Hz, 1H), 3.88 (dd, J = 2.4, 8.3 Hz, 1H), 3.80 (s, 3H), 3.50 (br, 1H), 2.49 (dd, J = 6.6, 14.5 Hz, 1H), 1.89 (dd, J = 5.0, 14.5 Hz, 1H), 1.45 (s, 3H), 1.41 (s, 3H), 1.36 (s, 3H), 1.35 (s, 3H). ^{13}C NMR ($CDCl_3$, 75 MHz): δ 169.8, 109.3, 109.1, 94.4, 73.8, 71.3, 70.8, 69.8, 67.0, 53.3, 32.6, 27.2, 27.1, 25.9, 25.5. IR (CH_2Cl_2): ν 3520, 3002, 2977, 1751, 1450 cm^{-1}. $[\alpha]^{22}_D$ +20.1 (*c* 0.25, CH_2Cl_2). HRMS (EI^+): calcd for $C_{15}H_{24}O_8$ $[M]^+$, 332.1471; found, 332.1473.

3-Deoxy-D-manno-2-octulosonic Acid (KDO), Ammonium Salt (2.NH_3). A solution of **41** (5.9 mg) in 90% aqueous acetic acid (5 mL) was heated to 90 °C for 45 min. Next, the mixture was concentrated in vacuo, and the residue was dissolved 0.1 M aqueous NaOH. The reaction was stirred at room temperature for 1 h, followed by the addition of Amberlyte IR-120$^+$. After the mixture was stirred for 30 min, the ion-exchange resin was filtered off, and concentrated ammonia was added to obtain a pH of 11. The mixture was again stirred for 30 min, after which the solvent was evaporated, yielding the ammonium salt of **2** (4.2 mg, 99%). As expected,[2,25] the ^1H NMR spectrum in D_2O showed a complicated mixture of the α- and β-furanose and -pyranose forms, as well as traces of lactone forms. The spectrum and the optical rotation agreed with those of a purchased sample and with literature data: $[\alpha]^{22}_D$ +38.8 (*c* 0.4, H_2O) [purchased sample $[\alpha]^{22}_D$ +38.0 (*c* 0.5, H_2O); lit.[25a] $[\alpha]^{21}_D$ +39.5 (*c* 1.2, H_2O)].

Acknowledgment. This research has been financially supported (in part) by the Council for Chemical Sciences of The Netherlands Organization for Scientific Research (CW-NWO). Irmgard Henning is acknowledged for kindly performing several reactions. Christien A. Schortinghuis (Chiralix B.V., Nijmegen, The Netherlands) is acknowledged for kindly providing the preparative HPLC separations.

Supporting Information Available: Experimental procedures and/or spectroscopic and analytical data including NMR spectra for compounds **1**, **2**, **4**, **9**, **10**, **13**−**16**, **21**−**33**, **36**−**39**, **41**. This material is available free of charge via the Internet at http://pubs.acs.org.

JO060913X

(28) Norbeck, D. W.; Kramer, J. B.; Lartey, P. A. *J. Org. Chem.* **1987**, *52*, 2174.